

CLAIMS AMENDMENT

1-22. (canceled)

23. (currently amended): A hybrid modular polyketide synthase (PKS) comprising at least a first naturally occurring extender module and a second naturally occurring extender module of a different PKS from said first module,

wherein said extender modules are defined as consisting of the amino acid sequence from the N-terminus of the ketosynthase (KS) domain through the C-terminus of the acyl transferase protein (ACP) domain;

wherein the C-terminus of said first module is covalently linked to the N-terminus of a naturally occurring intra-molecular linker (RAL) ~~or inter-molecular linker (ERL)~~ and the N-terminus of the second module is covalently linked to the C-terminus of said RAL~~[[~~or ERL~~]]~~, and

wherein said RAL is defined as the amino acid sequence between the C-terminus of an upstream ACP domain and the N-terminus of an adjacent downstream KS domain; said ACP and KS domains occupying adjacent modules in the same reading frame;

wherein either said first module or second module is not covalently linked to said RAL ~~[[~~or ERL~~]]~~ in a naturally occurring polyketide synthase;

whereby the RAL effects the transfer of a nascent polyketide chain from said first module to said second module ~~is facilitated~~.

24. (canceled)

25. (previously presented): The hybrid modular PKS of claim 23 wherein said RAL is selected from the group consisting of M2 *ery*, M4 *ery*, M6 *ery*, M2 *rif*, M3 *rif*, M5 *rif*, M3 *rap*, M4 *rap*, and M7 *rap* intra-module linkers (SEQ. ID. NO's: 3-11, respectively).

26-27. (canceled)

28. (previously presented): The hybrid modular PKS of claim 23 which contains *ery* modules 1 and 3 through 6 inclusive and tylosin module 2, and wherein said polyketide chain is transferred from *ery* module 1 to *tyl* module 2 and then to *ery* modules 3 through 6 inclusive.

29. (previously presented): The hybrid modular PKS of claim 23 which contains *ery* modules 1 through 5 inclusive and narbomycin module 6, wherein said polyketide chain is transferred from *ery* modules 1 through 5 inclusive to *nar* module 6.

30. (previously presented): The hybrid modular PKS of claim 23 which contains modules 1 and 3 through 6 inclusive of *ery* and modules 2-3 of tylosin, spiramycin or niddamycin, wherein said polyketide chain is transferred from *ery* module 1 to modules 2-3 of tylosin, spiramycin or niddamycin and then to *ery* modules 3 through 6 inclusive.

31. (previously presented): The hybrid modular PKS of claim 23 which contains modules 1 through 3 inclusive of tylosin, spiramycin or niddamycin and modules 3 through 6 inclusive of *ery*, and wherein said polyketide chain is transferred from modules 1 through 3 inclusive of said tylosin, spiramycin or niddamycin to *ery* modules 3 through 6 inclusive.

32. (previously presented): The hybrid modular PKS of claim 23 which contains a module of tylosin, spiramycin or niddamycin and modules 1-2 and 3 through 6 inclusive of *ery*, wherein said polyketide chain is transferred from *ery* modules 1-2 to the tylosin, spiramycin or niddamycin module and then to *ery* modules 3 through 6 inclusive.

33. (previously presented): The hybrid modular PKS of claim 23 which contains modules 1 and 3 through 6 inclusive of *ery* and module 5 of tylosin, spiramycin or niddamycin having the enoyl reductase catalytic activity inactivated, wherein said polyketide chain is transferred from *ery* module 1 to module 5 of tylosin, spiramycin or niddamycin and then to *ery* modules 3 through 6 inclusive.

34. (previously presented): The hybrid modular PKS of claim 23 which contains *ery* modules 1 through 4 inclusive and 6 and module 6 of spiramycin or niddamycin, wherein said polyketide chain is transferred from *ery* modules 1 through 4 inclusive to module 6 of spiramycin or niddamycin and then to *ery* module 6.

35. (previously presented): The hybrid modular PKS of claim 23 which contains module 1 of FK-506 or 520 and modules 2 through 14 inclusive of rapamycin, wherein said polyketide chain is transferred from module 1 of FK-506 or 520 and then to modules 2 through 14 inclusive of rapamycin.

36. (previously presented): The hybrid modular PKS of claim 23 which contains module 1 and 11 through 14 inclusive of rapamycin and modules 2 through 6 inclusive of FK-506 or 520 wherein said polyketide chain is transferred from module 1 of rapamycin to modules 2 through 6 inclusive of FK-506 or 520 and then to modules 11 through 14 inclusive of rapamycin.

37. (previously presented): The hybrid modular PKS of claim 23 which contains module 1 of rapamycin, modules 2 through 7 inclusive of FK-506 or 520 and modules 12 through 14 inclusive of rapamycin, wherein said polyketide chain is transferred from module 1 of rapamycin to modules 2 through 7 inclusive of FK-506 or 520 and then to modules 12 through 14 inclusive of rapamycin.

38. (previously presented): The hybrid modular PKS of claim 23 which contains module 1 of rapamycin, modules 2 through 8 inclusive of FK-506 or 520 and modules 13-14 of rapamycin, wherein said polyketide chain is transferred from module 1 of rapamycin to modules 2 through 8 inclusive of FK-506 or 520 and then to modules 13-14 of rapamycin.

39. (previously presented): The hybrid modular PKS of claim 23 which contains modules 1 through 10 inclusive of rapamycin and modules 7 through 10 inclusive of FK-506 or 520, wherein said polyketide chain is transferred from modules 1 through 10 inclusive of rapamycin to modules 7 through 10 inclusive of FK-506 or 520.

40-44. (canceled)

45. (new): A hybrid modular polyketide synthase (PKS) comprising at least a first naturally occurring extender module and a second naturally occurring extender module of a different PKS from said first module,

wherein said extender modules are defined as consisting of the amino acid sequence from the N-terminus of the ketosynthase (KS) domain through the C-terminus of the acyl transferase protein (ACP) domain;

wherein the C-terminus of said first module is covalently linked to the N-terminus of a naturally occurring inter-molecular linker (ERL) and the N-terminus of the second module is covalently linked to the C-terminus of said ERL,

wherein said ERL is defined as the amino acid sequence beginning at the C-terminus of the ACP domain of the most downstream module of a first open reading frame and the amino acid sequence upstream of the N-terminus of the most upstream KS domain of a second open reading frame of a naturally occurring PKS, which second open reading frame is immediately adjacent to and downstream of said first open reading frame; and

wherein either said first module or second module is not covalently linked to said ERL in a naturally occurring polyketide synthase;

whereby the ERL effects the transfer of a nascent polyketide chain from said first module to said second module.

46. (new): The hybrid modular PKS of claim 45 wherein the portion of the ERL at the N-terminus of the second module is selected from the group consisting of SEQ. ID. NO's: 12-19, respectively.

47. (new): The hybrid modular PKS of claim 45 which contains *ery* modules 1 and 3 through 6 inclusive and tylosin module 2, and wherein said polyketide chain is transferred from *ery* module 1 to *tyl* module 2 and then to *ery* modules 3 through 6 inclusive.

48. (new): The hybrid modular PKS of claim 45 which contains *ery* modules 1 through 5 inclusive and narbomycin module 6, wherein said polyketide chain is transferred from *ery* modules 1 through 5 inclusive to *nar* module 6.

49. (new): The hybrid modular PKS of claim 45 which contains modules 1 and 3 through 6 inclusive of *ery* and modules 2-3 of tylosin, spiramycin or niddamycin, wherein said polyketide chain is transferred from *ery* module 1 to modules 2-3 of tylosin, spiramycin or niddamycin and then to *ery* modules 3 through 6 inclusive.

50. (new): The hybrid modular PKS of claim 45 which contains modules 1 through 3 inclusive of tylosin, spiramycin or niddamycin and modules 3 through 6 inclusive of *ery*, and wherein said polyketide chain is transferred from modules 1 through 3 inclusive of said tylosin, spiramycin or niddamycin to *ery* modules 3 through 6 inclusive.

51. (new): The hybrid modular PKS of claim 45 which contains a module of tylosin, spiramycin or niddamycin and modules 1-2 and 3 through 6 inclusive of *ery*, wherein said polyketide chain is transferred from *ery* modules 1-2 to the tylosin, spiramycin or niddamycin module and then to *ery* modules 3 through 6 inclusive.

52. (new): The hybrid modular PKS of claim 45 which contains modules 1 and 3 through 6 inclusive of *ery* and module 5 of tylosin, spiramycin or niddamycin having the enoyl reductase catalytic activity inactivated, wherein said polyketide chain is transferred from *ery* module 1 to module 5 of tylosin, spiramycin or niddamycin and then to *ery* modules 3 through 6 inclusive.

53. (new): The hybrid modular PKS of claim 45 which contains *ery* modules 1 through 4 inclusive and 6 and module 6 of spiramycin or niddamycin, wherein said polyketide chain is transferred from *ery* modules 1 through 4 inclusive to module 6 of spiramycin or niddamycin and then to *ery* module 6.

54. (new): The hybrid modular PKS of claim 45 which contains module 1 of FK-506 or 520 and modules 2 through 14 inclusive of rapamycin, wherein said polyketide chain is transferred from module 1 of FK-506 or 520 and then to modules 2 through 14 inclusive of rapamycin.

55. (new): The hybrid modular PKS of claim 45 which contains module 1 and 11 through 14 inclusive of rapamycin and modules 2 through 6 inclusive of FK-506 or 520 wherein said polyketide chain is transferred from module 1 of rapamycin to modules 2 through 6 inclusive of FK-506 or 520 and then to modules 11 through 14 inclusive of rapamycin.

56. (new): The hybrid modular PKS of claim 45 which contains module 1 of rapamycin, modules 2 through 7 inclusive of FK-506 or 520 and modules 12 through 14 inclusive of rapamycin, wherein said polyketide chain is transferred from module 1 of rapamycin to modules 2 through 7 inclusive of FK-506 or 520 and then to modules 12 through 14 inclusive of rapamycin.

57. (new): The hybrid modular PKS of claim 45 which contains module 1 of rapamycin, modules 2 through 8 inclusive of FK-506 or 520 and modules 13-14 of rapamycin, wherein said polyketide chain is transferred from module 1 of rapamycin to modules 2 through 8 inclusive of FK-506 or 520 and then to modules 13-14 of rapamycin.

58. (new): The hybrid modular PKS of claim 45 which contains modules 1 through 10 inclusive of rapamycin and modules 7 through 10 inclusive of FK-506 or 520, wherein said polyketide chain is transferred from modules 1 through 10 inclusive of rapamycin to modules 7 through 10 inclusive of FK-506 or 520.